clinical symptoms or morphological abnormalities are immediately resolved with GC therapy in most patients, although relapse of the disease is frequent [2]. However, data on organ function in such patients are sparse.

In IgG4-related kidney disease (IgG4-RKD), IgG4-related tubulointerstitial nephritis (IgG4-TIN) is the most dominant feature [3, 4]. In our earlier study of IgG4-RKD, we found that most of the serological and radiological abnormalities and renal dysfunction mostly attributable to IgG4-TIN had improved at 1 month after the start of GC treatment in most patients [3–5]. However, renal function did not recover completely in patients with advanced renal damage. In 22 patients whose estimated glomerular filtration rate (eGFR) before treatment was <60 ml/min, there was a significant improvement of the eGFR at 1 month after the start of treatment (45.0 ± 13.8 ml/min, compared with 34.1 ± 15.8 ml/min before treatment, $p < 0.01$), but recovery of renal function reached a plateau during the initial 1 month of GC treatment in most patients, and thereafter renal atrophy developed in many [5]. In addition, relapse of the IgG4-related lesions occurred in 20 % of the patients with IgG4-RKD treated with GC [5]. These results raised certain questions, such as whether induction therapy with high-dose GC is superior in terms of initial recovery of renal function or relapse of IgG4-RKD in comparison with low-dose GC, or whether patients with pre-existing moderate to severe renal dysfunction will ultimately show progression to end-stage renal disease. Indeed, most of the patients with IgG4-related TIN showed high grades of fibrosis [6], and concerns about progression of fibrosis in IgG4-RD leading to irreversible organ dysfunction have been discussed, although data on organ function are sparse [7]. In the present study, we retrospectively examined differences in recovery of renal function or IgG4-RKD relapse according to the dose of GC used for induction therapy and the long-term renal outcome in a large multi-center cohort of IgG4-RKD patients with renal dysfunction.

Materials and methods

Patients

From 16 collaborating institutions in Japan, we retrospectively collected 44 patients diagnosed as having definite IgG4-RKD, in whom eGFR before GC treatment had been less than 60 ml/min. The diagnosis of definite IgG4-RKD was based on the criteria proposed by the Japanese Society of Nephrology [4]. Among the 44 patients, 40 were diagnosed as having IgG4-RKD between January 2006 and April 2013. Four patients were initially diagnosed as having TIN accompanied by primary Sjögren's syndrome between 1995 and 2001, and the diagnosis was corrected to IgG4-TIN on the basis of histological and serological re-evaluation. Twenty-two of the 44 patients had been included in our earlier study [5]. In one patient with advanced renal failure, hemodialysis became necessary immediately after the start of treatment, and renal function did not recover thereafter. We excluded this patient and enrolled the remaining 43 for the present study. In our earlier study of IgG4-RKD, abnormalities of renal function, serological and imaging features, and extra-renal lesions were all improved at 1 month after the start of GC therapy in most patients, and renal function was maintained at a similar level at 12 months [5]. Therefore, in this study, we also retrospectively examined both treatment and renal function before therapy, 1 month after the start of treatment, 12 months after the start of treatment, at the last review, and at relapse of IgG4-RKD. The study was approved by the review board of Nagaoka Red Cross Hospital and the boards of the collaborating institutions as well as the ethics board of the Japanese Society of Nephrology. All data and samples from patients were collected with their informed, written consent, and the study was conducted in compliance with the principles of the Declaration of Helsinki.

Definition of remission of IgG4-RKD

Remission was decided on the basis of stabilization or improvement of renal function (as assessed in terms of the serum creatinine concentration or eGFR), improvement of radiological findings, and resolution of extra-renal manifestations [8–10].

Definition of relapse of IgG4-RKD

Relapse of IgG4-RKD was decided by each attendant physician on the basis of a rapid rise in the serum creatinine level, after careful exclusion of other renal diseases, with re-appearance or worsening of serologic, radiologic (including extra-renal lesions), or histologic features [5, 9]. In IgG4-RD, re-elevation of serological levels alone in the absence of clinical symptoms or abnormal imaging findings was not considered to be relapse because this can also occur when relapse is not evident [8, 9]. Also in our earlier study of IgG4-RKD, the serum IgG4 level remained elevated in 70.8 % of patients in remission [5]. Therefore, re-elevation of the serum level of IgG or IgG4 alone and worsening of urinalysis parameters alone were not considered to be relapse of IgG4-RKD.

Statistics

Statistical analysis was performed using SPSS version 19 software (IBM SPSS, Chicago, IL, USA). The significance

of differences between groups was determined using the paired Student's t test, Mann–Whitney U test, or Wilcoxon signed-rank test, and the significance of differences in frequencies was analyzed with Fisher's exact probability test. Data are presented as mean ± S.D. A probability of $p < 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics

Forty-three patients with definite IgG4-RKD and renal dysfunction who had been treated with GC were enrolled. Their eGFR before GC therapy had been less than 60 ml/min/1.73 m^2, and none had developed end-stage renal disease within the initial 1 month of therapy. The eGFR before GC therapy was 6.6–59.8 (mean 33.2) ml/min. The results of renal biopsy and the clinical course suggested that the renal dysfunction had been caused by IgG4-RKD (mainly IgG4-TIN). All of the 43 patients were Japanese (38 males and 5 females), and the age at the time of diagnosis of renal disease was 42–85 (mean 66.5) years. The follow-up period after GC treatment was 6–210 months (mean 43 months). Forty-one of the 43 patients (95.3 %) had accompanying IgG4-related extra-renal lesions, and the mean number of extra-renal organs involved was 2.4. In 40 patients, renal needle biopsy was conducted and IgG4-TIN was evident in all of them. In the remaining 3 patients, the diagnosis of IgG4-RKD was based on the characteristic features of the renal parenchyma demonstrated by radiology, in the setting of biopsy-proven IgG4-related lesions in extra-renal organs [4]. Glomerular lesions other than global sclerosis were evident in 7 patients in addition to IgG4-TIN. GC alone was used for induction therapy in all patients, although the dose was decided according to the opinion of each attending physician. The initial dose was continued for 2–4 weeks in all cases, and then tapered gradually to a maintenance dose (5–10 mg/day) in most cases. Forty-one of the patients (95.3 %) had been treated with GC alone during the clinical course. An immunosuppressant (azathioprine or cyclophosphamide) was added for 2 patients on maintenance. At the last review, 40 of the 43 patients had been maintained on low-dose GC.

Recovery of renal function for induction glucocorticoid therapy

Among the 43 patients, the initial dose of prednisolone employed was ≤0.6 mg/kg/day (0.2–0.6 mg/kg/day, mean 0.47 mg/kg/day) in 27 patients (group L), and >0.6 mg/kg/day (0.61–1.1 mg/kg/day, mean 0.81 mg/kg/day) in 16 patients (group H). The mean follow-up period was significantly longer in group H (85.6 months) than in group L (44.0 months) ($p < 0.05$). There was no significant intergroup difference in the other clinical parameters (Table 1). Glomerular lesions were evident in 4 patients in group L (segmental endocapillary proliferative glomerulonephritis in 1, IgA nephropathy in 1, membranoproliferative glomerulonephritis in 1, and diabetic nephropathy in 1), and 3 patients in group H (membranous nephropathy in 1, Henoch-Schönlein purpura nephritis in 1, and mesangioproliferative glomerulonephritis in 1).

At 1 month after the start of GC therapy, stabilization or improvement of renal function, improvement of radiological findings, and resolution of extra-renal manifestations were achieved in all 43 patients, i.e., all patients were judged to be in remission. In both groups, the pretreatment eGFR was significantly improved at 1 month after the start of GC therapy [33.0 ± 16.4–44.1 ± 15.4 ml/min in group L ($p < 0.01$) and 33.6 ± 14.2–46.4 ± 14.1 ml/min in group H ($p < 0.01$)], and reached a plateau thereafter (Fig. 1). The degree of improvement during the initial

Table 1 Baseline clinical features in group L and group H

	Group L ($n = 27$)	Group H ($n = 16$)	p
Age (years)	67.3 ± 9.9	65.1 ± 9.6	0.48
Male	24 (88.9)	14 (87.5)	0.89
Hypertension	15 (55.6)	10 (62.5)	0.66
Diabetes mellitus	16 (59.3)	9 (56.3)	0.85
Serum IgG4 level (mg/dl)	1067.7 ± 751.4	1050.1 ± 574.7	0.93
Hypocomplementemia	13 (48.1)	9 (56.3)	0.61
Extra-renal lesion (s)	25 (92.6)	15 (93.8)	0.89
Number of extra-renal lesions	2.6 ± 1.6	2.1 ± 1.3	0.30
Pretreatment eGFR (ml/min/1.73 m^2)	33.0 ± 16.4	33.6 ± 14.2	0.91
Follow-up periods (months)	44.0 ± 21.0	85.6 ± 63.8	0.027
Initial prednisolone dose (mg/kg daily)	0.47 ± 0.11	0.81 ± 0.16	<0.001

Values for categorical variables are given as number (percentage), values for continuous variables are given as mean ± standard deviation

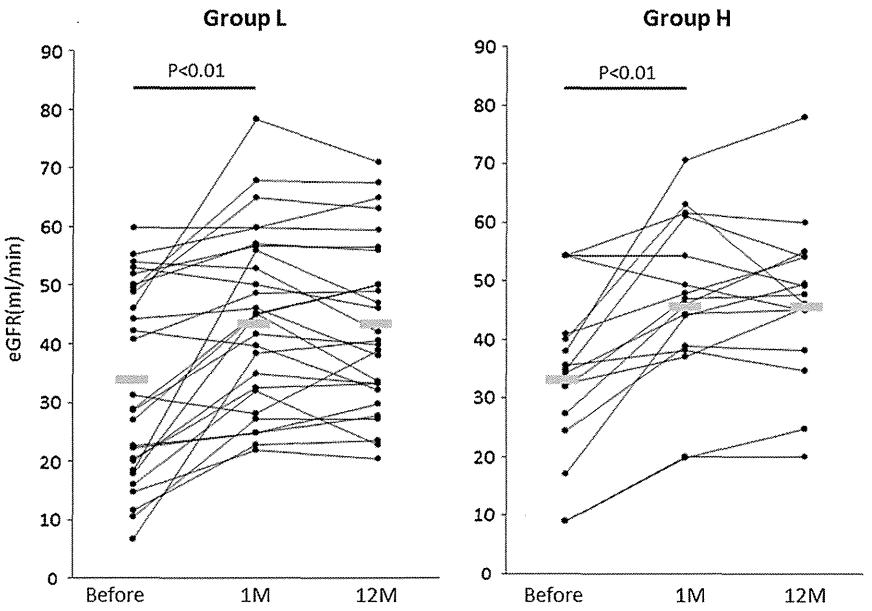

Fig. 1 Changes in eGFR after GC therapy. Individual plots of eGFR before GC treatment (Before), at 1 month after the start of treatment (1 M) and at 12 months after the start of treatment (12 M). The mean values at each point are shown adjacent to the *horizontal gray bars*

1 month of GC therapy showed no significant inter-group difference (11.1 ± 11.9 ml/min in group L, 12.8 ± 10.5 ml/min in group H, $p = 0.63$).

Relapse of IgG4-RKD in patients who had been maintained on glucocorticoid

We examined relapse of IgG4-RKD in 39 patients who had been followed up for over 12 months and had been maintained on GC at the last review. Relapse of IgG4-RKD occurred in 6 patients (4 in group L and 2 in group H) who had been receiving 2.5–10 mg prednisolone daily, and the relapse rate did not differ significantly between group L [4 of 24 (16.7 %)] and group H [2 of 15 in group H (13.3 %)] ($p = 0.78$). All of the 6 relapsed patients were elderly males with several extra-renal lesions, and eGFR before therapy had varied from 6.6 to 54.0 ml/min. Relapse occurred at 22, 18, 12, and 14 months after the start of GC therapy in group L, and at 12 and 16 months after the start of GC therapy in group H; there were no striking inter-group differences in the clinical features of the relapsed patients. In all cases of IgG4-RKD relapse, increasing the dose of GC was effective for resolution. Relapse of extra-renal lesions occurred in 2 patients (type 1 autoimmune pancreatitis and sialadenitis) in group L and 1 patient (lymphadenopathy) in group H.

Long-term renal outcome of patients who had been maintained on glucocorticoid

Thirty-two of the 43 patients were followed up for over 36 months after GC therapy. Among them, 29 had been maintained with low-dose GC at the last review (Table 2), and these patients were followed up for 37–210 months (mean 74 months). Fifteen of these 29 patients had been included in our earlier study [5] (patients 2, 3, 5, 6, 7, 12, 15, 16, 18, 19, 23, 25, 26, 27, and 29) and 14 were newly enrolled for the present study. The mean maintenance prednisolone dose at the last review was 4.9 mg daily (range 1–10 mg daily, <5 mg daily in 76 %). Among the 29 patients, none showed progression to end-stage renal disease, and there was no significant difference in eGFR at the last review (43.5 ± 14.1 ml/min) in comparison to that at 1 month after the start of treatment (43.5 ± 14.4 ml/min) ($p = 0.85$) (Table 2). Although renal function gradually decreased in some patients, it was not considered to represent relapse of IgG4-RKD by each attendant physician.

Clinical course of patients in whom maintenance therapy was withdrawn

Maintenance therapy was withdrawn in 3 of the 43 patients. In 2 patients, maintenance GC was stopped according to the opinion of the attending physician at 24 and 36 months after the start of treatment, respectively, and the patients were followed without any maintenance therapy thereafter. At the last review (51 and 4 months after therapy withdrawal), no relapse of IgG4-RD, including IgG4-RKD, had occurred in these patients. In the remaining patient, pre-treatment eGFR (40 ml/min) had improved to 60 ml/min at 1 month after the start of GC therapy, but at 2 months the therapy was stopped at the patient's request because of an adverse event (severe infection). Five months after withdrawal of GC therapy, renal function deteriorated rapidly

Table 2 Long-term renal outcome of patients who had been maintained on glucocorticoid

Follow-up				Extra-renal lesions	Renal pathology	Initial PSL (mg/kg/day)	Last PSL (mg/day)	eGFR (ml/min)		
No	Age	Sex	(mo)					Before Tx	1 M after Tx	Last
1	68	M	37	Sa, RF	TIN	0.53	5	15.9	31.9	30.5
2	63	M	38	Sa, Pa, Lu, Ao	TIN	0.31	9	42.2	29.3	41.6
3	75	M	38	Sa	TIN	0.60	5	22.3	24.8	30.9
4	67	M	38	La, Lu, Ly	TIN	0.37	5	11.6	22.7	25.5
5	60	M	39	La, Sa	TIN	0.45	5	31.1	28.1	41.9
6	59	M	46	Sa, Pa, Pro, Ao	TIN	0.80	5	54.2	49.3	35.8
7	61	F	46	Ly, Lu	TIN	0.51	1	18.4	55.9	52.6
8	72	M	46	RF, Ao	TIN	0.60	5	20.4	32.5	36.7
9	63	F	46	La, Sa, Ly	TIN	0.60	8	28.9	45.1	41.5
10	61	M	47	Sa, Lu, Ly	TIN	1.00	10	34.9	61.0	54.4
11	60	M	48	Sa, RF, Pa	TIN	0.39	5	54.2	54.2	41.2
12	68	M	49	Sa, Ly	TIN + IgAGN	0.41	8	28.6	41.6	42.3
13	59	M	51	Ly	TIN	0.62	5	24.4	38.9	59.1
14	85	M	53		TIN	0.36	3.75	53.0	50.0	19.0
15	42	M	55	Sa, La, Pa, Lu	NA	0.51	3	59.8	56.8	58.3
16	75	F	56	Sa, Ly, Lu	TIN + HSPN	0.63	7	17.1	43.9	56.1
17	80	M	58		TIN	0.37	2.5	17.9	45.2	38.7
18	76	M	64	Sa	TIN + MN	0.68	5	8.9	19.7	25.7
19	58	M	66	He, Neu	TIN	0.54	7	45.4	56.8	66.3
20	85	M	67	Pro	TIN	0.26	2.5	14.7	21.8	16.6
21	71	M	71	Sa, Ly, Lu	TIN	0.45	8	46.1	78.4	71.2
22	62	F	74	La, Sa, Pa, RF	TIN	0.6	2	55.2	59.8	70.8
23	83	M	77		TIN + MN	0.85	4	35.5	38.1	30.3
24	84	M	91	Sa, Ly	TIN + MPGN	0.2	2.5	20.0	34.9	30.1
25	68	M	115	Sa	TIN	0.61	5	41.0	47.8	52.0
26	55	M	150	Sa, Pa	TIN	0.8	2	27.3	46.1	49.3
27	60	M	180	Sa, Ly	TIN + MGN	0.73	5	32.5	37.1	49.3
28	45	M	197	Pa	TIN	0.66	2.5	32.0	47.0	49.0
29	61	M	210	Sa, Ly, Pa, Thr	TIN	1.1	5	54.3	61.6	49.6

mo month, *PSL* dose of prednisolone, *Sa* sialadenitis, *RF* retroperitoneal fibrosis, *Pa* type 1 autoimmune pancreatitis, *Lu* lung lesion, *Ao* periaortitis, *La* dacryoadenitis, *Ly* lymphadenitis, *Pro* prostatitis, *He* hepatopathy, *Neu* perineuritis, *Thr* thrombocytopenia, *TIN*; IgG4-related tubulointerstitial nephritis, *IgAGN* IgA nephropathy, *HSPN* Henoch-Schönlein purpura nephritis, *MN* membranous nephropathy, *MPGN* membranoproliferative glomerulonephritis, *MGN* mesangioproliferative glomerulonephritis, *NA* not available, *Tx* treatment

with re-elevation of the serum IgG4 level. Although relapse of IgG4-RKD was suspected, the patient developed infection several times, and was followed up without any immunosuppressive therapy, including GC, at the patient's request. At the last review (at 50-month follow-up), the eGFR was 24 ml/min.

Discussion

Although no formal treatment strategy for IgG4-RD has yet been established, GC is used for first-line therapy in most patients [1, 2], and a moderate dose GC is now recommended for initial treatment of type 1 autoimmune pancreatitis [11, 12]. However, there has been a tendency to use high-dose GC for induction therapy in patients with multi-organ damage or organ failure, because of an underlying unfounded belief that use of a lower dose may predispose to progression of organ damage, or frequent relapse. IgG4-TIN is characterized by a dense lymphoplasmacytic infiltrate and characteristic and high-grade fibrosis [6, 13]. Histologically, IgG4-TIN may appear potentially serious because severe inflammation and marked fibrosis is usually associated with progressive and irreversible organ failure, and in fact renal dysfunction can occur in the absence of therapy [3–5]. In addition, the level of serum IgG4 is highly elevated and multiple organs are affected in most patients with IgG4-TIN [3, 4]. Therefore,

high-dose GC had been used as induction therapy for IgG4-TIN, especially at the initial stage after discovery of the disease. However, as prednisolone 0.6 mg/kg/day has been widely employed by Japanese physicians for initial therapy of type 1 autoimmune pancreatitis [11], moderate or relatively small doses of GC have also been tried as induction therapy for IgG4-TIN, even in the absence of any evidence for its effectiveness. In the present study, we found that there was no significant difference in the rate of IgG4-RKD (mostly IgG4-TIN) relapse or recovery of renal function during the initial 1 month of GC therapy between group L (initial dose of prednisolone <0.6 mg/kg/day, mean 0.47 mg/kg/day) and group H (>0.6 mg/kg/day, mean 0.81 mg/kg/day), suggesting that high-dose GC is not necessary, and that a prednisolone dose of 0.5 mg/kg/day is sufficient for induction therapy in IgG4-TIN patients with renal dysfunction. In addition, we found that once renal function had recovered during the first month of GC therapy, it could be maintained for a long period on low-dose GC maintenance therapy alone (mostly less than 5 mg prednisolone daily) in IgG4-TIN.

Although the pathogenesis of IgG4-RD has not been clarified, "storiform fibrosis" has been described as a characteristic feature [14]. This is manifested as a swirling pattern of fibrosclerosing inflammation consisting of inflammatory cells and irregular fibrosis, i.e., fibrosis containing many inflammatory cells but lacking genuine fibrosis [15]. Indeed, in most patients with IgG4-TIN, nests of inflammatory cells surrounded by irregular fibers in the renal interstitium are evident by PAM staining [16], and the pattern of fibrosis is quite different from that in other types of TIN [6]. In addition to this unique inflammatory process in IgG4-RD, the epithelium is relatively well preserved in spite of severe inflammation [15]. Also in IgG4-TIN, severe tubulitis is rare [6]. These features may account for the rapid response of IgG4-TIN to GC therapy and relatively good maintenance of renal function under maintenance therapy, rather than severe inflammation and high-grade fibrosis. Of course, some fibrotic lesions may progress to genuine fibrosis with fewer cellular components, as described for type 1 autoimmune pancreatitis [15], and this can be observed radiologically as gradual progression of renal atrophy. In fact, re-biopsy studies of IgG4-TIN after GC therapy have revealed a mixture of almost normal areas and severely fibrotic areas in the same patient [17]. Also, follow-up CT studies of IgG4-RKD patients after GC have revealed areas showing complete recovery admixed with regions of progressive atrophy in some cases [17, 18].

Although GC is quite an effective treatment for IgG4-TIN, withdrawal may be difficult if GC is being used as monotherapy, although this has not yet been confirmed. Relapse of IgG4-RKD occurred in about 15 % of the present patients, even those being maintained on GC, and progression of renal dysfunction was apparent in 1 of 3 patients after withdrawal of maintenance therapy. Although an increase in the dose of GC is usually effective for treatment of IgG4-RKD relapse [5], and further development to end-stage renal disease is rare, our earlier study indicated that long-term use of GC was associated with various adverse events such as worsening of diabetes mellitus, avascular necrosis of the femoral head and osteoporosis [5], and therefore another treatment strategy should also be considered. Although various immunosuppressive drugs such as azathioprine or mycophenolate mofetil have been tried as steroid-sparing therapy for IgG4-RD, no immunosuppressive drug has been shown to be definitely effective for reduction of the maintenance dose or withdrawal of GC [19, 20]. Recently, B cell depletion therapy (rituximab) for IgG4-RD has been proposed by the North American group, with reduction or withdrawal of maintenance GC, or even monotherapy without GC [21], although data for IgG4-RKD are sparse.

Because this study was retrospective, the most appropriate dose of GC as induction therapy for IgG4-TIN patients remained unclear. Prednisolone at 0.2–0.3 mg/kg/day was effective for recovery of renal function in a few of the present patients, suggesting that a smaller GC dose might also be effective. Further prospective studies will be necessary to determine the most appropriate induction dose of GC for IgG4-TIN.

In addition, glomerular lesions in some cases of IgG4-RKD should be considered when formulating any treatment strategy. In the present study, although patients with glomerular lesions also achieved remission at 1 month after the start of GC treatment, the response in terms of urinalysis parameters after therapy varied, in contrast to the uniform rapid response in terms of renal function, radiology, and serology [5]. In fact, development of end-stage renal disease has been described in patients with IgG4-related membranous glomerulonephritis [22].

In conclusion, our present study has revealed that rapid recovery of renal function can be achieved with a relatively small dose of GC monotherapy in most IgG4-RKD patients, and that recovery of renal function can be maintained for a long period on low-dose GC maintenance in patients for whom induction GC therapy has been successful, although relapse can occur even in patients receiving maintenance therapy. These observations should be informative for establishment of a useful treatment strategy for IgG4-RD and also for considering its pathogenesis.

Acknowledgments This work was supported in part by grants from Health and Labour Sciences Research Grants for the Study of Intractable Disease from Ministry of Health, Labor and Welfare, Japan and 'IgG4-related Kidney Disease' working group of the Japanese Society of Nephrology. We are grateful to Drs. S Koide,

N Hayami, T Takata, T Nishino, I Osawa, K Hiromura, H Adachi, T Kaneko, S Tanaka, Y Matsumoto, R Furuya, Y Kadoya, C Kitabayashi and K Yoshita for providing data on their patients.

Compliance with ethical standards

Conflict of interest None of the authors declare any conflicts of interest.

References

1. Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol. 2012;22:1–14.
2. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366:539–51.
3. Saeki T, Nishi S, Imai N, et al. Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. Kidney Int. 2010;78:1016–23.
4. Kawano M, Saeki T, Nakashima H, et al. Proposal for diagnostic criteria for IgG4-related kidney disease. Clin Exp Nephrol. 2011;25:810–9.
5. Saeki T, Kawano M, Mizushima I, et al. The clinical course of patients with IgG4-related kidney disease. Kidney Int. 2013;84:826–33.
6. Yoshita K, Kawano M, Mizushima I, et al. Light-microscopic characteristics of IgG4-related tubulointerstitial nephritis: distinction from non-IgG4-related tubulointerstitial nephritis. Nephrol Dial Transplant. 2012;27:2755–61.
7. Khosroshahi A, Wallace ZS, Crowe JL, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol. 2015. [Epub ahead of print].
8. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. Gut. 2009;58:1504–7.
9. Chari ST, Murray JA. Autoimmune pancreatitis, part II: the relapse. Gastroenterology. 2008;134:625–8.
10. Nachman PH, Hogan SL, Jennette JC, et al. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiits and glomerulonephritis. J Am Soc Nephrol. 1996;7:33–9.
11. Kamisawa T, Okazaki K, Kawa S, et al. Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013 III. Treatment and prognosis of autoimmune pancreatitis. J Gastroenterol. 2014;49:961–70.
12. Hart PA, Kamisawa T, Brugge WR, et al. Long-term outcomes of autoimmune pancreatitis: a multicenter, international analysis. Gut. 2013;62:1771–6.
13. Saeki T, Kawano M. IgG4-related kidney disease. Kidney Int. 2014;85:251–7.
14. Deshpande V, Zen Y, Chan JKC, et al. Consensus statement on the pathology of gG4-related disease. Mod Pathol. 2012;25:1181–92.
15. Notohara K. Pathology. In: Kamisawa T, Chung JB, editors. Autoimmune pancreatitis. Heidelberg: Springer; 2015. p. 23–30.
16. Yamaguchi Y, Kanetsuna Y, Honda K, et al. Characteristic tubulointerstitial nephritis in IgG4-related disease. Hum Pathol. 2011;43:536–49.
17. Mizushima I, Yamada K, Fujii H, et al. Clinical and histological changes associated with corticosteroid therapy in IgG4-related tubulointerstitial nephritis. Mod Rheumatol. 2012;22:859–70.
18. Kawano M, Saeki T. IgG4-related kidney disease—an update. Curr Opin Nephrol Hypertens. 2015;24:193–201.
19. Ebbo M, Daniel L, Pavic M, et al. IgG4-related systemic disease: features and treatment response in a French cohort: results of a multicenter registry. Medicine (Baltimore). 2012;91:49–56.
20. Khosroshahi A, Carruthers MN, Deshpande V, et al. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine (Baltimore). 2012;91:57–66.
21. Carruthers MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis. 2015;. doi:10.1136/annrheumdis-2014-206605.
22. Alexander MP, Larsen CP, Gibson IW, et al. Membranous glomerulonephritis is a manifestation of IgG4-related disease. Kidney Int. 2013;83:455–62.

Japan College of Rheumatology
MODERN RHEUMATOLOGY

http://informahealthcare.com/mor
ISSN 1439-7595 (print), 1439-7609 (online)

Mod Rheumatol, 2015; Early Online: 1–3

DOI: 10.3109/14397595.2015.1069951

Taylor & Francis
Taylor & Francis Group

RAPID COMMUNICATION

Validation of the comprehensive diagnostic criteria for IgG4-related disease in a SMART registry

Motohisa Yamamoto[1], Yui Shimizu[1], Hidetaka Yajima[1], Tetsuya Tabeya[2], Chisako Suzuki[1], Yasuyoshi Naishiro[1], Kenichi Takano[3], Rieko Murakami[4], Saho Honda[4], Takashi Abe[5], Tetsuo Himi[3], Masaya Mukai[6], and Hiroki Takahashi[1]

[1]*Division of Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan,* [2]*Department of Internal Medicine, Otaru General Hospital, Japan,* [3]*Department of Otolaryngology, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan,* [4]*Department of Internal Medicine and Rheumatology, JR Sapporo Hospital, Japan,* [5]*Department of Gastroenterology, Kushiro City General Hospital, Kushiro, Hokkaido, Japan, and* [6]*Division of Rheumatology and Clinical Immunology, Department of Medicine, Sapporo City General Hospital, Sapporo, Hokkaido, Japan,*

Keywords

Comprehensive diagnostic criteria, IgG4-related disease, Mikulicz's disease, Validation

History

Received 13 April 2015
Accepted 4 June 2015

Introduction

Immunoglobulin (Ig)G4-related disease (IgG4-RD) is a systemic, chronic inflammatory disorder that was established in Japan this century. IgG4-related dacryoadenitis and sialadenitis, also known as Mikulicz's disease, and type 1 autoimmune pancreatitis are representative IgG4-RDs. The pathology can cause irreversible dysfunction in the kidneys, lungs, retroperitoneal cavity, thyroid gland, and prostate gland [1]. For this reason, early therapeutic intervention is necessary [2]. Diagnosis is therefore very important. For this purpose, the comprehensive diagnostic criteria for IgG4-RD, developed in 2011 [3], and the clinical diagnostic criteria for specific organ involvements of IgG4-RD can be used [4–8]. The comprehensive diagnostic criteria consist of enlargement of the involved organs, elevated levels of serum IgG4, and marked infiltration of IgG4-bearing plasmacytes into the involved organs. We can diagnose cases satisfying all these criteria as "definite" IgG4-RD. When only physical/imaging findings and histopathological findings are satisfied, the case is defined as "probable' IgG4-RD." Cases with physical/imaging findings and serological findings represent "possible" IgG4-RD. Four years have passed since the comprehensive diagnostic criteria were established, and they have been confirmed as useful for the diagnosis of IgG4-RD. However, no validation of the criteria has been performed. We therefore validated the 2011 comprehensive diagnostic criteria for IgG4-RD using a SMART (Sapporo Medical University and related institutes database for investigation and best treatment for IgG4-RD) registry cohort [9].

Correspondence to: Motohisa Yamamoto, Division of Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine. South 1- West 16, Chuo-ku, Sapporo, Hokkaido, 0608543, Japan. Tel: +81-11-611-2111. Fax: +81-11-611-2282. E-mail: mocha@cocoa.plala.or.jp

Methods and materials

The validation cohort consisted of 48 cases with IgG4-RD as the final diagnosis and 5 cases in which IgG4-RD was ruled out. Cases with IgG4-RD had been suspected as having IgG4-RD and introduced to our hospital and the related institutes since 2012 (after proposal of the comprehensive diagnostic criteria for IgG4-RD), and were followed up for 1 year. Exclusion of the disorders written in the exemption at the comprehensive diagnostic criteria was carefully implemented. Non-IgG4-RD cases were also followed up for 1 year, and the diagnosis was confirmed. We analyzed the implementation and results of imaging and serological and histopathological examinations, and validated the comprehensive diagnostic criteria for IgG4-RD using this cohort. However, we did not consider other organ-specific diagnostic criteria for IgG4-RD in this analysis. Written consent to use the information from these cases was obtained from all patients in accordance with the Declaration of Helsinki. This study proceeded under the approval of our institutional review board (SMU 22-57, 24-155).

Results

Cases with IgG4-RD comprised 30 males and 18 females. Mean (± standard deviation [SD]) age at first visit was 64.0 ± 10.7 years. Mean level of serum IgG4 was 678.4 ± 513.0 mg/dL. The involved organs were as follows: salivary glands in 42 cases, lacrimal glands in 31 cases, kidneys in 12 cases, retroperitoneal fibrosis in 11 cases, pancreas in 6 cases, and lungs in 2 cases. Enlarged organs were observed in all cases, and elevated levels of serum IgG4 were detected in 46 cases (positivity rate, 95.8%). One of the remaining 2 patients presented with gradual increases in serum IgG4 levels. Histopathological examination was performed in 37 cases (examination rate, 77.1%), but 6 cases presented with infiltrating IgG4/IgG-positive cells < 40% in the involved organs. The ratio of positive results was 83.8% (Table 1). The first diagnosis was

Table 1. Ratio of implementation and positivity in image, serological, and histopathological examination in IgG4-related disease.

	Physical and image Ex.	Serological Ex.	Histopathological Ex.
No. of Ex. Implemented	48	48	37
Ratio of implementation	100.0%	100.0%	77.1%
No. of positivity	48	46	31
Ratio of positivity	100.0%	95.8%	83.8%

Ex. Examination, *No.* number.

as follows: 30 definite cases; 1 probable case; 16 possible cases; and 1 denial case. The denial case later presented with increased levels of serum IgG4. The only possible case in which biopsy could not be performed presented with malignant lymphoma. For this reason, the counts for final diagnosis were unchanged. On the other hand, non-IgG4-RD cases comprised 2 cases with

Table 2. Background of the validation cohort in the SMART registry.

		Case		Lesions	Serum levels of IgG4	Physical & image findings	Serological findings	Pathological findings	Biopsied organ	Diagnosis	Remarks
IgG4-RD	1	74	F	L, S, P	963	○	○	○	SM	Definite	
	2	72	M	L, S, P, K, Lu, R, Pr	2120	○	○	○	L	Definite	
	3	77	M	L, S, Pi	406	○	○	×	M	Possible	
	4	55	F	L, S, P, K	870	○	○	○	SM	Definite	
	5	47	F	L, S, K	263	○	○	○	L	Definite	
	6	69	M	L, S, R	1420	○	○	○	SM	Definite	
	7	49	F	L, S, R, M	726	○	○	○	L	Definite	
	8	81	F	L, S, P	196	○	○	○	SM	Definite	
	9	77	F	L, S	757	○	○	○	SM	Definite	
	10	37	M	L, S	340	○	○	N.D.		Possible	
	11	64	M	L, S, K, R, Pr	2210	○	○	○	SM	Definite	
	12	68	M	L, S, K	911	○	○	○	SM	Definite	
	13	60	F	L, S	293	○	○	○	SM	Definite	
	14	65	F	L, S	130	○	×	×	L	Denial	IgG4 elevated later
	15	51	F	L, S	768	○	○	○	SM	Definite	
	16	65	M	L, S	257	○	○	○	SM	Definite	
	17	57	M	L, S	402	○	○	○	SM	Definite	
	18	58	F	L, S, K, R	1290	○	○	N.D.		Possible	
	19	64	M	L, S, R	1410	○	○	○	SM	Definite	
	20	58	M	L, S, R	1220	○	○	N.D.		Possible	Lymphoma developed later
	21	66	M	L, S	225	○	○	○	L	Definite	
	22	67	M	L, S, P	626	○	○	○	SM	Definite	
	23	63	F	L, S, P	712	○	○	○	L	Definite	
	24	69	M	L, S	309	○	○	○	SM	Definite	
	25	48	F	L, S	223	○	○	×	SM	Possible	
	26	54	F	S	185	○	○	×	SM	Possible	
	27	56	M	S, K, Pr	305	○	○	○	K	Definite	
	28	71	M	S, R	210	○	○	N.D.		Possible	
	29	74	M	S, R	374	○	○	○	SM	Definite	
	30	40	M	S, K	243	○	○	N.D.		Possible	
	31	80	M	S	612	○	○	○	L	Definite	
	32	65	M	S	548	○	○	○	SM	Definite	
	33	81	M	S	252	○	○	N.D.		Possible	
	34	62	M	S, K	774	○	○	○	SM	Definite	
	35	75	F	S	790	○	○	N.D.		Possible	
	36	66	M	S, Lu, R	672	○	○	N.D.		Possible	
	37	64	M	S, K	1690	○	○	○	SM	Definite	
	38	59	F	S	73	○	×	○	SM	Probable	
	39	77	M	S	744	○	○	○	SM	Definite	
	40	79	M	S, K	1060	○	○	N.D.		Possible	
	41	69	M	S, K	1700	○	○	○	SM	Definite	
	42	79	M	S	353	○	○	×	SM	Possible	
	43	51	F	L	190	○	○	○	L	Definite	
	44	66	M	L	604	○	○	N.D.		Possible	
	45	64	M	L	392	○	○	×	L	Possible	
	46	60	F	L	608	○	○	N.D.		Possible	
	47	49	M	L, R	551	○	○	○	L	Definite	
	48	69	F	L	586	○	○	○	L	Definite	
Non-IgG4	1	61	M		6	○	×	×		Denial	Lymphoma
	2	71	F		19	○	×	×		Denial	Lung cancer
	3	74	M		4	○	×	×		Denial	Lymphoma
	4	42	M		165	○	○	×		Possible	Castleman's disease
	5	69	M		555	×	○	×		Denial	Colon cancer

L lacrimal gland, *S* salivary gland, *SM* submandibular gland, *M* minor salivary gland, *P* pancreas, *K* kidney, *Lu* lung, *R* retroperitoneal fibrosis, *Pr* prostate gland, *Pi* pituitary gland, *N.D.* not done.

Table 3a. CDC and the final diagnosis. A. Analysis with all cases ($n = 53$), B. Analysis with definite and probable cases ($n = 35$).

A			
All cases		Final diagnosis	
CDC	N = 53	IgG4-RD	Non IgG4-RD
	Satisfied	47	1
	Not satisfied	1	4
B			
Definite and probable cases		Final diagnosis	
CDC	N = 35	IgG4-RD	Non IgG4-RD
	Satisfied	31	0
	Not satisfied	0	4

CDC, comprehensive diagnostic criteria.

malignant lymphoma, and 1 case each with multicentric Castleman's disease, lung cancer, and colon cancer. In this group, 4 cases showed positive physical/imaging findings, and 2 cases showed positive serological findings. Histopathological findings were not positive in any cases. Collating these data with the comprehensive diagnostic criteria, the case with multicentric Castleman's disease was substantially considered a possible case of IgG4-RD, but histopathological examination denied a diagnosis of IgG4-RD. The remaining 4 cases were denied, and diagnosis was unchanged after a year (Table 2).

Next, we validated the 2011 comprehensive diagnostic criteria for IgG4-RD using this validation cohort. Analysis with all cases offered 97.9% sensitivity and 80.0% specificity. The positive and negative predictive values were 97.9% and 80.0%, respectively. The efficiency rate was 96.2%. In the analyses with definite and probable cases (i.e., after excluding possible case), sensitivity and specificity were both 100.0% (Table 3a and b).

Discussion

We validated the 2011 comprehensive diagnostic criteria for IgG4-RD with a SMART registry cohort in multiple centers after 2012. This represents the first report of validation of the comprehensive diagnostic criteria for IgG4-RD. Analysis with all cases offered 97.9% sensitivity and 80.0% specificity. It is considered that both sensitivity and specificity are more increased because we routinely confirm whether the cases, which are not satisfied with the comprehensive diagnostic criteria, are matched with the organ-specific diagnostic criteria for IgG4-RD in everyday practice. The results also disclosed the extremely high usefulness of the criteria for "definite" and "probable" cases, but showed that other diseases might be assessed as "possible" cases of IgG4-RD. We encountered a case of lymphoma that was first diagnosed as a "possible" case in the absence of histopathological examination. Since lymph node biopsy revealed no IgG4-positive cells at the diagnosis of malignant lymphoma, this case was considered to not represent IgG4-RD from the first. On the other hand, a case with multicentric Castleman's disease also satisfied the criteria for "possible" IgG4-RD, but the lymph node specimen denied the diagnosis of IgG4-RD in this case. These cases reveal that histopathological examination is very important in the diagnosis of IgG4-RD. Since cases with malignancies including lymphoma, Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, granulomatosis with polyangiitis, sarcoidosis, and eosinophilic granulomatosis with polyangiitis might satisfy these criteria, we have to carefully differentiate these pathologies from IgG4-RD clinically and histopathologically. To be excessively particular about the values of serum IgG4 and the number of IgG4-positive cells in the involved tissues might lead to misdiagnosis. In daily practice, we often encounter patients presenting with swollen organs and elevated levels of serum IgG4, and recommend histopathological examination. The cases will be "definite" or "possible" cases. Rare "probable" cases are encountered, satisfying the histopathological criteria with or without meeting serological criteria. How this inclination influences the accuracy of diagnostic criteria remains unclear at this point. International validation of these criteria is necessary in the future. The subjects of this study were mainly the cases with IgG4-related dacryoadenitis and sialadenitis. There are several organ lesions, which are difficult for the biopsy in IgG4-RD. We have to validate the comprehensive diagnostic criteria subsequently in the other organ lesions and solve the above problems.

We validated the comprehensive diagnostic criteria for IgG4-RD using the data of a SMART registry, which was composed of IgG4-related dacryoadenitis and sialadenitis. It was shown that the comprehensive diagnostic criteria for IgG4-RD were useful for the Japanese cases with IgG4-related dacryoadenitis and sialadenitis.

Table 3b. The sensitivity, specificity, and efficiency rate of CDC for IgG4-related disease.

Subject	All cases	Definite & Probable cases
Sensitivity	97.9%	100.0%
Specificity	80.0%	100.0%
Efficiency rate	96.2%	100.0%

Conflict of interest

None.

References

1. Yamamoto M, Takahashi H, Shinomura Y. Mechanisma and assessment of IgG4-related disease: lessons for the rheumatologist. Nat Rev Rheumatol. 2014;10(3):148–59.
2. Shimizu Y, Yamamoto M, Naishiro Y, Sudoh G, Ishigami K, Yajima H, et al. Necessity of early intervention for IgG4-related disease–delayed treatment induces fibrosis progression. Rheumatology (Oxford). 2013; 52(4):679–83.
3. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012;22(1):21–30.
4. Yamamoto M, Takahashi H, Shinomura Y. Mikulicz's disease and the extraglandular lesions. Curr Immunol Rev. 2011;7(2):162–71.
5. The Japan Pancreas Society, the Ministry of Health and WelfareInvestigation Research Team for Intractable Pancreatic Disease. Suizo. 2012;27(1):17–25. (In Japanese with English abstract).
6. Kawano M, Saeki T, Nakashima H, Nishi S, Yamaguchi Y, Hisano S, et al. Proposal for diagnostic criteria for IgG4-related kidney disease. Clin Exp Nephrol. 2011;15(5):615–26.
7. Ohara H, Okazaki K, Tsubouchi H, Inui K, Kawa S, Kamisawa T, et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci. 2012;19(5):539–42.
8. Goto H, Takahira M, Azumi A. Japanese study Group for IgG4-Related Ophthalmic Disease. Jpn J Ophthalmol. 2015;59(1):1–7.
9. Yamamoto M, Yajima H, Takahashi H, Yokoyama Y, Ishigami K, Shimizu Y, et al. Everyday clinical practice in IgG4-related dacryoadenitis and/or sialadenitis: results from the SMART database. Mod Rheumatol. 2015;25(2):199–204.